Attorney Docket No.: VGEN.P-056

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Darasch, et al.	Serial No.:	09/536,111
Filed:	March 24, 2000	Confirmation No.:	2310

For: Method for Alignment of DNA Sequences with Increased Read-Length and Accuracy

BRIEF FOR APPELLANT and APPENDIX, EXTENSION OF TIME

Mail Stop: Appeal Brief - Patents
Honorable Commissioner for Patents
P O Box 1450
Alexandria, VA 22313-1450

Sir:

Enclosed are:

3 copies - Appeal Brief and Appendix (13 pages each)
Petition For (2-Month) Extension of Time (PTO/SB/22)
Credit Card Payment Form (PTO-2038) ($730.00)

If necessary, the Commissioner is authorized to debit any additional fees deemed due from Deposit Account No. 15-0610.

Respectfully,

OPPEDAHL & LARSON LLP

Marina T. Larson, Ph.D., PTO Reg. No. 32,038
P.O. Box 5068
Dillon, CO 50435-5068
Tel: (970) 468-6600
Fax: (970) 468-0104

CERTIFICATE OF MAILING under 37 CFR § 1.8(a)

I hereby certify that this paper and its attachments mentioned herein, are being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop: Appeal Brief - Patents, Honorable Commissioner for Patents, P O Box 1450, Alexandria, VA 22313-1450, on August 1, 2003.

August 1, 2003
Date of Signature

Mary Winston

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Darasch	
Application No.: 09/536,111	
Filed: March 24, 2000	Group Art Unit: 1631
Title: Method for Alignment of DNA Sequences with Increased Read-Length and Accuracy	Examiner: L. Clow
Attorney Docket No.: VGEN.P-056	Confirmation No.: 2310

BRIEF FOR APPELLANT

This brief is filed in support of Applicants' Appeal from the final rejection mailed September 26, 2003. Consideration of the application and reversal of the rejections are respectfully urged.

Real Party in Interest

The real party in interest is Bayer Healthcare LLC, which has acquired the assignee, Visible Genetics Inc.

Related Appeals and Interferences

To Applicants' knowledge, there are no related appeals or intereferences.

Status of Claims

Claims 1-22 are pending and are the subject of this appeal. No other claims have been presented.

Status of Amendments

All amendments have been entered.

Summary of Invention

When determining the sequence of DNA molecule, it is common practice to prepare sets of fragments of DNA, each set reflecting in the lengths of the fragments the positions of one of the four bases, A, C, G and T, that make up DNA. These sets of fragments are evaluated by electrophoresis to determine the size of the fragments in the set, and hence the positions of each base in the sequence. While this process is elegant and even simple in theory, experimental variability observed in actual practice makes automation of the process difficult because the peaks associated with different size fragments do not resolve at the regular spacing which theory would predict, and in fact sometimes overlap to such an extent that it is difficult to determine the order of bases. The present invention provides one method to assign correct base numbers to observed peaks in these electrophoresis traces to facilitate automated sequencing.

As set forth in the claim 1, one aspect of the present invention is directed to a method for assignment of base numbers to peaks within an experimental DNA sequencing data trace derived from the separation of experimental DNA sequencing fragments. This method comprises the steps of:

(a) obtaining one or more reference DNA sequencing data traces derived from the separation of reference DNA sequencing fragments reflecting the position of at least one base in a reference polynucleotide of known sequence;

(b) evaluating the reference DNA sequencing data traces to determine a corrected time scale indicative of migration times at which peaks should occur;

(c) sampling the experimental DNA sequencing data trace at time points determined by the corrected time scale, and

(d) assigning a base number to each peak found in the experimental DNA sequencing data trace based upon the corrected time scale. When this method is performed for sufficient species of bases, the sequence of the target nucleotide is determined. (Claim 11). Claims 21 and 22 are directed to apparatus, which receives input concerning electrophoresis traces, and comprises processors programmed to perform the method of the invention.

Issues on Appeal

1. Are claims 1-22 anticipated by US Patent No. 6,303,303 of Green et al?

2. Are claims 21 and 22 properly rejected for obviousness-type double patenting over claims 1-14 of Green et al?

Appellants submit that both of these questions should be answered in the negative.

Grouping of Claims

The claims are argued as several distinct groups that do not stand or fall together. As is apparent from the discussion below, this is appropriate because the dependent claims contain limitations not found in the independent claims and which the Examiner has not identified as being taught by the allegedly anticipatory Green reference. Thus:

Claims 1, 4, 9-11, 15, 20 and 21 are argued as a first group.

Claims 2, 5, 12, 16 and 22 are argued as a second group.

Claim 3, 13 and 14 are argued as a third group.

Claims 6-8 and 17-19 are argued as a fourth group.

Argument

Anticipation

Claims 1-22 are rejected by the Examiner as anticipated under 35 USC § 102(e) by US Patent No. 6,303,303 of Green et al. In order to justify an anticipation rejection, the law requires that the single reference relied upon teach each and every element of the claimed invention. Failure to disclose even a single element requires that the reversal of the rejection. In the present case, the reference fails to disclose several limitations found in each and every claim. In addition, the Examiner has not addressed limitations in dependent claims, and these limitations are also not disclosed. Thus, reversal of the rejection is appropriate.

Claims 1, 11 and 21 Are Not Anticipated

Claim 1 recites a method for assigning base numbers to electrophoresis peaks. Claim 11 recites a method for evaluating the sequence of a target polynucleotide. While the specific limitations in these claims will be discussed below in detail, and compared to the Green patent, it is informative to start by looking at the differences between the inventions of this and the Green patent.

The present invention makes use of a reference data trace which is collected using the same apparatus, subject to the same experimental variations as the experimental data traces. The reference data trace is derived from the samples of known sequence, but this sequence need bear no relationship to the experimental sequence being determined. This means, as an important consequence, that the methodology of this application can be employed when the nature of the DNA being sequenced is not known.

It is well known in the art that the time-spacing between peaks is not constant over a sequencing run, and further that it can vary from lane to lane of a sequencing gel. The reference trace in the method of the present invention is evaluated to determine where the peaks are located, and thus to determine the times at which peaks should occur in an experimental data trace run under the same conditions. The experimental data traces are then evaluated at these times to see if peaks are present. For example, if one knows that from the reference trace that base number 100 is represented by a peak at time X, then one can look at the experimental data trace(s) at time X and assign whatever peak is found there as base 100 in the experimental sequence.

In contrast, in the Green patents, the standard data trace is one which should (absent mutation or error) be the same as the experimental fragment. The Green method can only be performed where the user knows what the material being sequenced is. The analysis of the two traces (standard and experimental) is done to determine the stretching and shifting which is needed to make the experimental trace look like the standard. Thus, in Green, a polynomial function is determined to define the stretching and shifting which is needed to make the

experimental trace look like the standard trace. In the Green patents, there is no analysis of the standard data trace to find the times at which peaks actually occur and thus the times at which peaks should occur in an experimental data trace run under the same conditions. There is also no use of a defined time scale to sample for peaks.

The Examiner has oversimplified and mischaracterized claim 1 by stating that all that is required in the present claims is that "experimental data be compared to a reference trace taken at a time location." This statement is incorrect in several respects. First of all, in the present invention, there is no **comparison** between the reference trace and the experimental data trace as that term is used in Green. There is only the identification of a list of times that correspond to peak locations from the reference trace and the use of these times to direct sampling of the experimental trace(s). Second, the isolated steps of Green that happen to use similar words like "time," do not equal that which is claimed.

For example, step (b) of claims 1 and 11 reads:

> (b) evaluating the reference DNA sequencing data traces to determine a corrected time scale **indicative of migration times at which peaks should occur**.

The Examiner has not pointed to where in the Green patent this step is performed, and cannot do so because no such step is performed. Green does not identify the locations (i.e., the times) of peaks in the standard)or reference) data trace and does not determine a corrected time scale based on the positions of peaks in the reference data trace. Indeed, notwithstanding the Examiner's statement (without citation, Office Action of September 26, 2002, Page 3) that Green teaches "normalization of spacing between peaks using a second order polynomial to give a corrected time scale," the words "corrected" and "time scale" appear nowhere in the Green Patent. This is not surprising since Green has nothing to do with correction of time scale, but rather with using the second order or higher polynomial to make two fragments look alike (regardless of the time scale). Furthermore, this process is performed as a modification to the experimental data trace. The present invention does not rely on changing the experimental data trace, but instead uses the reference data trace to establish specific windows in time in which to look for peaks in the experimental data trace.

The Examiner also incorrectly asserts that "all that is disclosed includes 'sampling the experimental data trace(s) at time points.'" Claims 1 and 11, however say more than this. Step (c) reads: "sampling the experimental DNA sequencing data trace(s) at time points **determined by the corrected time scale**" which is the corrected time scale determined in step (b) that says where the peaks ought to be. In assessing anticipation, the Examiner may not choose to omit words from the claim, and then say that the revised limitation is met. It is the entire claim that must be found in the reference cited.

Claim 21 recites an apparatus for performing the method of claim 1. The claim recites processor components programmed to accomplish each of the method steps set forth in claim 1. The failure of the Examiner to show that these steps are taught in Green means that there is no teaching of an apparatus to perform these steps.

The rejection of claims 1, and 21, and claims 4, 9, 10, 15, and 20 dependent thereon, should therefore be reversed.

Claims 2, 12, and 22 Are Not Anticipated

Notwithstanding the submission of specific argument concerning additional limitations in claims 2 and 12, the Examiner has never addressed these limitations and said where they are found in the Green patent. Appellants submit that these limitations are also lacking, and that the rejection of this claim is therefore separately reversible.

Claim 2 reads:

> 2. The method of claim 1, wherein the step of evaluating the reference DNA sequence data traces includes the steps of:
>
> (i) identifying a plurality of peaks in the reference DNA sequencing data traces, and creating a data table containing the number of each peak based on the known sequence of the polynucleotide, and the position of each peak in the reference DNA sequencing data trace;
>
> (ii) identifying a set of coefficients for a polynomial effective to substantially linearize a plot of peak number versus separation between adjacent peaks; and
>
> (iii) creating from the coefficients and the polynomial a corrected time scale which reflects the positions at which a peak should occur at any given point in a sequencing data trace.

The same limitations are found in claim 12. Green does not disclose making a data table. Green does not disclose making a plot of peak number versus peak separation for the reference trace. Green does not disclose linearizing such a plot, and specifically does not disclose identifying a set of coefficients to linearize such a plot. And Green does not even mention a corrected time scale.

Claim 22 recites an apparatus for performing the method of claim 2. The claim recites processor components programmed to accomplish each of the method steps set forth in claim 2. The failure of the Examiner to show that these steps are taught in Green means that there is no teaching of an apparatus to perform these steps.

Thus, the rejection of claims 2, 12 and 22, and claims 5 and 16 dependent thereon, should be reversed for these additional reasons.

Claims 3, 13 and 14 Are Not Anticipated

Claims 3, 13 and 14 specify that the reference data trace and the experimental data trace are derived from analysis of sequencing fragments in a common lane of a sequencing gel. This is not disclosed in Green. In fact, Green indicates that the standard fragment pattern used in the Green methodology is suitably a typical pattern selected from among many trial runs, or a mathematical average of several trial runs. ('303 Patent, Col. 6, lines 23-39). Thus, the limitation of claims 3, 13 and 14 is not taught in the Green Patent, and these claims are separately distinguishable from the cited reference. The rejection of these claims should therefore be reversed.

Claims 6-8 and 17-19 Are Not Anticipated

Claims 6 and 17 recite the evaluation of a defined number of bands (or peaks) from each of the references DNA sequencing traces for use in determining the times at which the experimental data trace will be inspected for the presence of a peak. Claim 7 and 18 specify that this number is from 3-40. Claim 8 and 19 specify that the number is at least equal to the order of

the polynomial employed to linearize the plot of peak number versus separation between adjacent peaks. None of these limitations are found in the Green patent. To the contrary, the Green patent adjusts the experimental data trace to make it look like a standard trace, and there is no teaching that the standard trace is linearized. Accordingly, the rejection of claims 6-8 and 17-19 should be reversed.

Claims 21 and 22 Are Not Properly Rejected
For Obviousness-Type Double Patenting

The Examiner rejected claims 21 and 22 for obviousness-type double patenting in view of apparatus claims 1-14 of the Green Patent. The Examiner has not actually compared the limitations of the claims, but has made a general statement, namely that "the apparatus of Green can perform all of the limitations set forth in the instant application" without explanation of how this could be the case. The data processing portion of claim 1 of Green reads as follows:

> (d) means for causing the computer processor to determine one or more normalization coefficients for the experimental fragment pattern, said normalization coefficients being selected to provide a high degree of overlap between a normalized fragment pattern obtained by applying the normalization coefficients to the experimental fragment pattern and the standard fragment pattern.

This limitation calls for processing in which coefficients are found to make an experimental fragment pattern look like a standard fragment pattern. In contrast, claim 21 requires that the processor be programmed to perform very different functions: namely (1) "to evaluate the reference DNA sequencing data traces to determine a corrected time scale indicative of migration times at which peaks should occur;" (2) "to sample the experimental DNA sequencing data traces at time points determined by the corrected time scale" and (3) to assign a base number to each peak found in the experimental DNA sequencing data traces based upon the corrected time scale, thereby obtaining information about the sequence of the target polynucleotide. The Examiner has not said how a processor programmed to identify a polynomial that will make two data traces look alike can be assumed to be able to determine a corrected time scale for one trace alone, or to direct the sampling of the other trace at the time points identified by that time scale. Thus, for

these reasons, as discussed more fully above, there is no relationship between the apparatus of claims 21 and 22 and the apparatus of Green except the trivial similairty that they are both data processing apparatus.

Applicants would further point out that the Examiner has not explained why a double patenting rejection of this type is properly imposed when the document which is relied upon is available as prior art against the application. The historic rationale of obviousness-type double patenting is to prevent a party from getting a second patent on an obvious variant of an earlier-patented invention, where the earlier patent is not available as prior art against the claims, for example because it from the same inventors. On the other hand, where the prior patent is available as art, imposition of a rejection for obviousness-type double patenting places a commonly owned application on a worse footing than an application owned by an unrelated third-party. This is contrary to the purpose of the double-patenting provisions. Thus, the rejection should be reversed for this additional reason.

Respectfully submitted,

Marina T. Larson Ph.D.
PTO Reg. No. 32,038
Attorney for Applicant
(970) 468-6600

APPENDIX OF CLAIMS ON APPEAL

1. A method for assignment of base numbers to peaks within one or more experimental DNA sequencing data traces derived from the separation of experimental DNA sequencing fragments, comprising the steps of:

(a) obtaining one or more reference DNA sequencing data traces derived from the separation of reference DNA sequencing fragments reflecting the position of at least one base in a reference polynucleotide of known sequence;

(b) evaluating the reference DNA sequencing data traces to determine a corrected time scale indicative of migration times at which peaks should occur;

(c) sampling the experimental DNA sequencing data trace(s) at time points determined by the corrected time scale, and

(d) assigning a base number to each peak found in the experimental DNA sequencing data trace(s) based upon the corrected time scale.

2. The method of claim 1, wherein the step of evaluating the reference DNA sequence data traces includes the steps of:

(i) identifying a plurality of peaks in the reference DNA sequencing data traces, and creating a data table containing the number of each peak based on the known sequence of the polynucleotide, and the position of each peak in the reference DNA sequencing data trace;

(ii) identifying a set of coefficients for a polynomial effective to substantially linearize a plot of peak number versus separation between adjacent peaks; and

(iii) creating from the coefficients and the polynomial a corrected time scale which reflects the positions at which a peak should occur at any given point in a sequencing data trace.

3. The method of claim 1, wherein the experimental DNA sequencing data traces and a first reference DNA sequencing data trace are derived from analysis of sequencing fragments in a common lane of a sequencing gel.

4. The method of claim 1, wherein a plurality of reference DNA sequencing data traces are obtained, each derived from the separation of the same set of reference DNA sequencing fragments.

5. The method of claim 2, wherein the polynomial is a third or higher order polynomial.

6. The method of claim 2, wherein a defined number of bands are selected for evaluation from each of the reference DNA sequencing data traces.

7. The method of claim 6, wherein the defined number of bands selected is from 3 to 40.

8. The method of claim 6, wherein the defined number of bands is at least equal to the order of the polynomial, plus 1.

9. The method of claim 1, wherein base numbers are assigned to peaks within a plurality of experimental DNA sequencing data traces derived from the separation of experimental DNA sequencing fragments indicative of the positions of a plurality of types of bases.

10. The method of claim 9, wherein base numbers are assigned to peaks within four experimental DNA sequencing data traces derived from the separation of experimental DNA sequencing fragments indicative of the positions of four types of bases.

11. A method for evaluating the sequence of a target polynucleotide, comprising the steps of:

(a) obtaining one or more experimental DNA sequencing data traces derived from the separation of experimental DNA sequencing fragments reflecting the position of at least one base in the target polynucleotide and one or more reference DNA sequencing data traces derived from the separation of reference DNA sequencing fragments reflecting the position of at least one base in a reference polynucleotide of known sequence;

(b) evaluating the reference DNA sequencing data traces to determine a corrected time scale indicative of migration times at which peaks should occur;

(c) sampling the experimental DNA sequencing data traces at time points determined by the corrected time scale, and

(d) assigning a base number to each peak found in the experimental DNA sequencing data traces based upon the corrected time scale, thereby obtaining information about the sequence of the target polynucleotide.

12. The method of claim 11, wherein the step of evaluating the reference DNA sequence data traces includes the steps of:

(i) identifying a plurality of peaks in the reference DNA sequencing data traces, and creating a data table containing the number of each peak based on the known sequence of the polynucleotide, and the position of each peak in the reference DNA sequencing data trace;

(ii) identifying a set of coefficients for a polynomial effective to substantially linearize a plot of peak number versus separation between adjacent peaks; and

(iii) creating from the coefficients and the polynomial a corrected time scale which reflects the positions at which a peak should occur at any given point in a sequencing data trace.

13. The method of claim 11, wherein the reference DNA sequencing traces and the experimental DNA sequencing data traces are derived from analysis of sequencing fragments in a common sequencing gel.

14. The method of claim 13, wherein the experimental DNA sequencing data traces and a first reference DNA sequencing data trace are derived from analysis of sequencing fragments in a common lane of the common sequencing gel.

15. The method of claim 11, wherein a plurality of reference DNA sequencing data traces are obtained, each derived from the separation of the same set of reference DNA sequencing fragments.

16. The method of claim 12, wherein the polynomial is a third or higher order polynomial.

17. The method of claim 12, wherein a defined number of bands are selected for evaluation from each of the reference DNA sequencing data traces.

18. The method of claim 17, wherein the defined number of bands selected is from 3 to 40.

19. The method of claim 17, wherein the defined number of bands is at least equal to the order of the polynomial, plus 1.

20. The method of claim 11, wherein base numbers are assigned to peaks within a plurality of experimental DNA sequencing data traces derived from the separation of experimental DNA sequencing fragments indicative of the positions of a plurality of types of bases.

21. An apparatus for evaluating the sequence of a target polynucleotide, comprising:

(a) an input for receiving information about one or more experimental DNA sequencing data traces derived from the separation of experimental DNA sequencing fragments reflecting the position of at least one base in the target polynucleotide and one or more reference DNA sequencing data traces derived from the separation of reference DNA sequencing fragments reflecting the position of at least one base in a reference polynucleotide of known sequence;

(b) a processor, operatively programmed to evaluate the reference DNA sequencing data traces to determine a corrected time scale indicative of migration times at which peaks should occur;

(c) a processor, operatively programed to sample the experimental DNA sequencing data traces at time points determined by the corrected time scale;

(d) a processor, operatively programmed to assign a base number to each peak found in the experimental DNA sequencing data traces based upon the corrected time scale, thereby obtaining information about the sequence of the target polynucleotide; and

(e) an output for communicating the information about the sequence of the target polynucleotide.

22. The apparatus of claim 21, wherein the processor programmed to evaluate the reference DNA sequence data traces is programmed to perform the steps of:

(i) identifying a plurality of peaks in the reference DNA sequencing data traces, and creating a data table containing the number of each peak based on the known sequence of the polynucleotide, and the position of each peak in the reference DNA sequencing data trace;

(ii) identifying a set of coefficients for a polynomial effective to substantially linearize a plot of peak number versus separation between adjacent peaks; and

(iii) creating from the coefficients and the polynomial a corrected time scale which reflects the positions at which a peak should occur at any given point in a sequencing data trace.